CHRONIC TOXICITY SUMMARY

ETHYLENE DIBROMIDE

(1,2-dibromoethane; dibromoethane; alpha, beta-dibromoethane; EDB; ethylene bromide; glycol bromide)

CAS Registry Number: 106-93-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.8** m**g/m^3** (0.1 ppb)
Critical effect(s)	Decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities in human males
Hazard index target(s)	Reproductive system

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless, heavy, nonflammable liquid with a mildly sweet, chloroform-like odor.
Molecular formula	$C_2H_4Br_2$
Molecular weight	187.88 g/mol
Boiling point	131-132°C
Melting point	9.9°C
Vapor pressure	0.11 torr at 20°C
Solubility	Slightly soluble in water (3400 mg/L water at 20°C). Miscible with most organic solvents.
Conversion factor	7.68 µg/m^3 per ppb at 25°C

III. Major Uses and Sources

Ethylene dibromide (EDB) is used as a solvent for resins, gums, and waxes, and as a chemical intermediate in the synthesis of dyes and pharmaceuticals (HSDB, 1995). EDB was once widely used as a fumigant for the control of pests in the U.S. Because of concerns regarding its carcinogenicity, the agricultural uses of EDB were banned in 1983 (RECT, 1988). EDB was also commonly used as a gasoline additive to scavenge inorganic lead compounds. The transition to the use of lead-free gasoline has drastically curtailed the use of EDB in this country (REPROTOX, 1995). EDB is now used mainly in industry. EDB may be formed naturally in the ocean as a result of macro algae growth. Exposure to the general population, via inhalation,

may occur in the vicinity of industries and in industrial settings where this compound is manufactured and used. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1179 pounds of EDB (CARB, 2000).

IV. Effects of Human Exposures

Pharmacokinetic studies of EDB in humans could not be found in the literature. However, *in vitro* studies of EDB metabolism in human liver samples have been performed (Wiersma *et al.*, 1986). These experiments have shown that the enzyme systems known to metabolize EDB in rodent liver also metabolize EDB in the human liver. EDB was metabolized by human liver cytosolic glutathione S-transferases (GST), microsomal GST, and microsomal mixed function oxidases (MFO). MFO activity resulted in adducts irreversibly bound to protein, while GST activity was mostly responsible for adducts irreversibly bound to DNA. Rodent liver enzymes similarly activate EDB to metabolites that bind to cellular macromolecules. In human fetal liver (16-18 weeks gestation) cytosolic GST was also found to metabolize EDB with high efficiency (Kulkarni *et al.*, 1992). Since detoxification via MFO activity may be limited at this stage of development, the results suggest that the human fetus and neonate may be at greater risk from EDB toxicity than adults.

A study of mortality from cancer and respiratory diseases was conducted among 161 employees exposed to EDB in 2 production units operated from 1942 to 1969 and from the mid-1920s to 1976, respectively (Ott *et al.*, 1980). No apparent connection was found between mortality due to respiratory diseases and exposure to EDB, when compared to U.S. white male mortality figures.

Due to the structural similarity of EDB to dibromochloropropane (DBCP), a known toxic agent in human male reproductive organs, a number of epidemiological studies concerning male reproduction and spermatogenesis were conducted.

In a study of 59 employees exposed to EDB at the Ethyl Corporation plant in Magnolia, Arkansas, the sperm counts of the exposed men were divided into 2 groups depending on estimated exposure (Ter Haar, 1980). Twenty percent of the low exposure group (<0.5 ppm) had sperm counts below 40 million, whereas 42% of the high exposure group (0.5 to 5 ppm) had sperm counts below this figure. The sperm counts were intermediate between counts reported for 2 types of U.S. samples (for normal men). The observed births among the two exposure groups were found to be similar to the number of expected births. The author determined that EDB had no effect on sterility or reproduction in the workers. Weaknesses of this study include the small population of exposed workers and the lack of a concurrent unexposed control group. Taking these defects of the study into account, Dobbins (1987) concluded that the results provide evidence that EDB exposure between 0.5 and 5.0 ppm is associated with lower sperm counts.

A comparison of observed marital fertility with expected fertility (based on U.S. fertility rates) was conducted among 297 men working at 4 U.S. plants that manufacture EDB (Wong *et al.*, 1979). Fertility was 20% below expected for the four plants combined. This was largely due to

one plant (plant D), which was 49% below the expected level. After omitting the incidence of vasectomies and hysterectomies among married couples, observed fertility was still 39% below the expected figure for plant D but was now no longer statistically significant. Exposure levels of EDB at plant D were not known but were estimated to be no more than 5 ppm. Later review determined that expected (control) levels of fertility and the power of the study were too low, resulting in the inability to identify a possible adverse effect (Dobbins, 1987). The lower fertility at plant D indicates that EDB has the potential to reduce fertility, but the extent of the reduction cannot be estimated from this study. Further treatment of the data by a method that uses the proper statistical adjustments of reproductive experience in the U.S. population (used as the control) suggests borderline significance for reduced fertility among the combined workers at the four plants (Wong *et al.*, 1985). The fertility evaluation indicates that more in-depth epidemiologic or physiologic studies are needed.

Semen analysis of 83 pineapple workers at two plantations was performed by Rogers and associates (1981). EDB-exposed workers were removed from each group and placed in a separate group. The remaining two groups of workers acted as control groups. Sperm counts, motility, and morphology were similar among the three groups. However, 43.8% of exposed workers had abnormally low counts (<40 million/ml), while abnormally low sperm counts of controls were 34.2% and 17.8%. Of the four exposed workers that had fertility tests done, all tested in the infertile range. Forty percent or less tested in the infertile range among the control groups. The results suggest that workers exposed to EDB had reduced sperm counts, but exposure levels were not known.

Semen analysis among 46 men employed in the papaya fumigation industry was conducted to determine if EDB affected semen quality (Ratcliff *et al.*, 1987; Schrader *et al.*, 1987). Average duration of exposure was 5 years and the geometric mean breathing zone exposure to airborne EDB was 88 ppb (8 hr time weighted average) with peak exposures of up to 262 ppb. The comparison group consisted of 43 unexposed men from a nearby sugar refinery. Following consideration of confounding factors, statistically significant decreases in sperm count/ejaculate, the percentage of viable and motile sperm, and increases in the proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) were observed among exposed men. Semen pH was significantly more alkaline than that of unexposed workers. Other measured sperm quality parameters were unchanged. This study suggests that EDB can result in reproductive impairment. However, no measurement of male fertility was conducted.

In a study that examined similar indices of semen quality, 6 week exposure of 10 forestry workers to EDB (60 ppb time weighted average, with peak exposures of up to 2165 ppb) resulted in decreased semen volume and slower sperm velocity (Schrader *et al.*, 1988). Six unexposed men were used as controls. The researchers suggest that short-term exposure to EDB results in decreased sperm velocity, while long-term exposure, as in the previous study of EDB-exposed papaya workers, results in sperm immotility and cell death.

V. Effects of Animal Exposures

EDB is readily and rapidly absorbed from the lung when breathed as a vapor, from the GI tract when taken orally, or through the skin when applied dermally (HSDB, 1995). In rats, the rate of absorption of EDB from the respiratory tract reached a plateau within 10 to 20 minutes following exposure to 75 ppm EDB for up to 2 hours (Stott and McKenna, 1984). About 58% of the EDB was absorbed. Intraperitoneal injection of [^{14}C]EDB into guinea pigs resulted in the highest concentrations in liver, kidneys, and adrenals (Plotnick and Conner, 1976). Sixty-five percent of the dose was excreted as metabolites in urine, 3% in feces, and 12% excreted unchanged in expired air. In rats, the highest concentrations of [^{14}C]EDB label were found in liver, kidney and spleen following an oral dose of 15 mg/kg body wt (Plotnick *et al.*, 1979). Studies with rats have provided evidence that 2 pathways of metabolic bioactivation exist for EDB (RECT, 1988). The oxidative pathway yields the metabolite 2-bromo-acetaldehyde, which is associated with cell macromolecule binding and liver damage. The conjugative pathway principally yields glutathione products, such as *S*-(2-bromoethyl)-glutathione, which are mainly responsible for DNA binding and mutagenesis. In rats, orally administered EDB is excreted primarily in the urine as mercapturic acid derivatives (Jones and Edwards, 1968). The biologic half-life for elimination of [^{14}C]EDB in rats is 5.1-5.6 hours (Watanabe *et al.*, 1978) and less than 48 hours in mice and guinea pigs (HSDB, 1995). Besides the small amount irreversibly bound to cell macromolecules and DNA, EDB shows little, if any, bioaccumulation in mammalian systems.

In a subchronic toxicity study of experimental animals, rats and guinea pigs were given EDB by oral administration for about 4 months (Aman *et al.*, 1946). Body weights and mortality of animals at or below an average daily dose of 40-50 mg/kg body wt-day were unaffected. However, only one control animal/species was used, the dosing regimen was not well described, and pathologic examination was apparently not performed.

Subchronic exposure of rats (20/sex/group) to 50 ppm EDB for as many as 63 seven-hour exposures in 91 days resulted in no significant change in body weights (Rowe *et al.*, 1952). Liver and kidney weights were increased in both sexes while testis weights were decreased in males. Also, lung weights in males were elevated and spleen weights in females were decreased. Histopathological examination revealed no changes. Guinea pigs (8/sex/group) subjected to as many as 57 seven-hour exposures of 50 ppm EDB in 80 days exhibited reduced body weights. Organ weights were unchanged, but microscopic examination of the livers showed slight central fatty degeneration. In kidneys, slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium were observed. Four rabbits exposed to 59 seven-hour sessions at 50 ppm in 84 days showed no signs of adverse effects. Clinical signs of monkeys exposed to 50 ppm EDB (49 seven-hour exposures in 70 days) included an ill, unkempt appearance and nervousness. Slight central fatty degeneration in livers was observed, but pathology was not seen in other tissues. Exposure of the same four species to 25 ppm EDB for up to 220 days (145 to 156 seven-hour exposures) showed no signs of adverse effects.

In a 13-week inhalation study, 5 Fischer 344 albino rats/group/sex and 10 B6C3F1 mice/group/sex were exposed to 0, 3, 15, or 75 ppm EDB for 6 hr/day, 5 days/week (Reznik *et al.*, 1980). At 75 ppm, rats and mice exhibited severe necrosis and atrophy of the olfactory epithelium in the nasal cavity. Squamous metaplasia, hyperplasia and cytomegaly of the

epithelium were also seen in nasal turbinates, larynx, trachea, bronchi, and bronchioles. Minor alterations were seen in the nasal cavity of only a few male and female rats at 15 ppm. No compound-related lesions were observed in the olfactory and respiratory epithelium at 3 ppm. No lesions were seen in other tissues at any dose.

In another 13-week inhalation study, 40 male and 20 female CDF(F344) rats/group were exposed to 0, 3, 10, or 40 ppm EDB 6 hr/day, 5 days/week (Nitschke *et al.*, 1981). Male rats in the 40 ppm group exhibited decreased weight gain throughout most of the exposure period. However, reduced weight gain was never more than 6-8% below control levels. With the exception of decreased specific gravity of urine in females of the 40 ppm group, no treatment-related changes were observed in any rat group with respect to urinalysis, hematology, and clinical chemistry. At the end of 13 weeks, relative liver and kidney weights of males exposed to 40 ppm EDB were significantly elevated, while relative liver weights of females in the two highest exposure groups were significantly elevated. Absolute liver weight of females in the 40 ppm group was also significantly elevated. Histopathological examination revealed lesions primarily confined to the anterior sections of the nasal turbinates. Hyperplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium were observed in nasal turbinates of rats exposed to 40 ppm EDB. Only slight epithelial hyperplasia of nasal turbinates was noted at 10 ppm. No treatment related effects were seen at 3 ppm. Livers of females in the 40 ppm group showed a slight increase in fat. After an 88 day recovery period, there was a reversion to normal of the nasal turbinates in all but one rat.

In what was originally scheduled to be a lifetime exposure study, 50 Osborne-Mendel rats/group/sex and 50 B6C3F1 mice/group/sex were administered EDB 5 days/week by gastric lavage over a substantial portion of their life-span (NCI, 1978). Twenty untreated controls/sex and 20 vehicle controls/sex of each species were included in the study. Rats received initial doses of 80 and 40 mg/kg body wt-day for the first 17 weeks. Due to high mortality, dosing of high dose rats was discontinued for 13 weeks and resumed on week 30 at 40 mg/kg body wt-day. In week 42, all intubations of low and high dose rats ceased for 1 week followed by 4 weeks of dose administration. All surviving, treated male rats were necropsied in week 49; all surviving, treated female rats were necropsied in week 61. The resulting time-weighted average dose over the test period was 38 and 41 mg/kg body wt-day for low and high dose males, respectively, and 37 and 39 mg/kg body wt-day for low and high dose females, respectively. Mice received initial doses of 120 and 60 mg/kg body wt-day. In weeks 11-13, high and low doses were increased to 200 and 100 mg/kg body wt-day, respectively. Original dose levels were resumed after week 13. At week 40, administration of EDB was decreased to 60 mg/kg body wt-day for high dose mice. EDB administration was discontinued at week 54 with necropsy occurring at week 78 for males and high dose females. Low dose female mice were observed for 37 weeks after intubation ceased. The resulting time-weighted average dose over the test period was 62 and 107 mg/kg body wt-day for low and high dose mice, respectively. In rats, clinical signs by week 5 included reddened ears and hunched back in all treatment groups. By week 10, all treated rats had reduced body weights ($\geq$10%). Both female and male rats exhibited dose-dependent mortality. Many of the deaths occurred during or shortly after intubation, suggesting an acute toxic reaction. Pathology revealed hyperkeratosis and acanthosis of the forestomach in high dose males and females and in one low dose female. A small number of rats in both treatment groups showed adrenal cortex degeneration and peliosis of the liver (hepatitis). Dosed males showed

early development of testicular atrophy. In mice, dose-related body weight reduction and mortality were observed. Clinical signs included alopecia, thin, hunched appearance, soft feces and body sores. Hyperkeratosis and acanthosis of the forestomach were seen in high dose male and female mice. One incidence each of hyperkeratosis (in a female) and acanthosis (in a male) was seen at the low dose. Splenic changes were present in high dose mice and testicular atrophy was present in high dose males.

In a long-term inhalation exposure study, F344 rats and $B6C3F_1$ mice were exposed to 0, 10, or 40 ppm EDB 6 hr/day, 5 days/week for up to 103 weeks (NTP, 1982). In male and female rats, the high dose groups had reduced body weights and increased mortality that began at about week 60. The treatment-related non-neoplastic pathology included hepatic necrosis (both sexes), epithelial hyperplasia and suppurative inflammation throughout the respiratory system (both sexes), and nephropathy (males only). Toxic nephropathy and mineralization were also seen in high dose female rats. Testicular degeneration and atrophy occurred with greater frequency in exposed rats and may be related to observed testicular tumors. Spermatic granulomas were also more frequently seen in high-dose males. Degeneration of the adrenal cortex appeared to be dose-related in females, but only one incidence each was seen in low and high dose males. Increased incidence of retinal atrophy was observed in exposed females. In mice, body weights were reduced at the high dose in both males and females. Many of the high dose animals exhibited a progressive weakness of the limbs or body during the second year. Increased mortality occurred in a dose-related manner in females and was significantly greater in low dose males. Non-neoplastic pathology included epithelial hyperplasia throughout the respiratory system and serous and suppurative inflammation of the nasal cavity in exposed mice. In all male mice, the principal cause of death was urinary bladder inflammation. However, bladder epithelial hyperplasia was only seen in exposed animals. An increased incidence of suppurative inflammation of the prostate was present but was also seen in controls. Dose-related spleen hematopoiesis was observed in females.

Another long-term inhalation study investigated the effects of 0 or 20 ppm EDB (7 hr/day, 5 days/week) on 48 Sprague-Dawley rats/sex/group for 18 months (Wong *et al.*, 1982). Significantly lower body weight gains (>10% difference from controls) occurred by the 15^{th} month in males, and by the 18^{th} month in females. Significantly reduced food consumption was not apparent. Increased mortality rates in both sexes occurred beginning in the 12^{th} month of EDB exposure. All hematological findings were within normal ranges. The only recorded non-neoplastic gross or microscopic finding was atrophy of the spleen in males, which may be related to tumor formation (hemangiosarcoma). The nasal cavity was not examined.

In a study of the effect of EDB on sperm production in bulls (Isreal-Friesian breed), 4 calves were fed 2 mg/kg body wt-day for 12 months (Amir and Volcani, 1965). The bulls were then given EDB in gelatin capsules every other day for 2-4 months longer. EDB did not appear to affect the growth, health, and libido of the bulls. However, semen density and motility were significantly lower compared to untreated control bulls of the same age. Many abnormal spermatozoa were also present in treated bulls. A NOAEL for this effect was apparently not determined. Cessation of EDB administration resulted in normal sperm within 10 days to 3 months. Further studies confirmed that EDB adversely affected sperm production without any other apparent effects on bulls (Amir and Volcani, 1967; Amir and Ben-David, 1973). However,

feeding rams 2-5 mg/kg body wt-day for 120 days did not result in any effect on sperm or on the health of the animal (Amir, 1991).

Female B6C3F1 mice (10/group) were given 31.25, 62.5, or 125 mg/kg EDB by gastric lavage 5 days/week for 12 weeks (Ratajzak *et al*., 1995). At the highest dose, EDB significantly prolonged intervals between estrus, decreased hemoglobin and hematocrit levels, and increased cholesterol, triglycerides, total protein, and albumin. The highest dose also caused an immunosuppressive effect by lowering the *in vitro* splenic lymphocyte response to T- and B-cell mitogens.

In a developmental toxicity study, 15-17 pregnant Charles River CD rats and 17-19 pregnant CD mice were exposed to 0, 20, 38, and 80 ppm EDB by inhalation 23 hr/day during days 6 to 16 of gestation (Short *et al.*, 1978). A significant increase in mortality occurred in adult rats exposed to 80 ppm EDB and in adult mice exposed to 38 and 80 ppm EDB. Mice exposed to the highest dose experienced 100% mortality. Reduced body weights and feed consumption occurred in both species at all doses tested. Fetal mortality was increased in rats at the highest dose and in mice at 38 ppm. Reduced fetal body weights occurred at 38 ppm in rats and at all exposure levels in mice. No anomalies were seen in rat fetuses. An increase in runts at 38 ppm and a dose-dependent increase in skeletal anomalies were observed among mouse fetuses. However, these anomalies were characteristic of delayed development and occurred at doses that adversely affected maternal welfare. Therefore, these effects are indicative of fetal toxicity rather than teratogenicity.

Male reproductive toxicity of EDB has been evaluated in some other experimental animals. New Zealand white rabbits, dosed subcutaneously with 0, 15, 30, or 45 mg/kg body wt-day, showed adverse effects at the highest dose (Williams *et al.*, 1991). Increased mortality, increased serum enzymes, and liver damage were observed at this dose level. With respect to sperm quality, sperm velocity, motility, and motion parameters were reduced at the highest dose. A dose related decrease in semen pH was also noted. However, male fertility and fetal structural development were unaffected.

A dominant lethal assay in mice was negative following a single intraperitoneal injection of 100 mg EDB/kg body wt (Barnett *et al.*, 1992). Germ cell tests did not indicate that EDB was a germ cell mutagen in male mice.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Ratcliff *et al.*, 1987
Study population	46 exposed men, 43 unexposed men; 89 total
Exposure method	Variable workplace breathing zone airborne exposure (88 ppb geometric mean 8-hour time weighted average (TWA) exposure with peak exposures up to 262 ppb)
Critical effects	Reproductive toxicity; decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) in human males
LOAEL	88 ppb
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day occupational inhalation exposure rate), 5 days/week
Exposure duration	Average, 4.9 years (with standard deviation of 3.6 years)
Average experimental exposure	31 ppb for LOAEL group (88 x 10/20 x 5/7)
Human equivalent concentration	31 ppb
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies factor	1
Intraspecies factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.1 ppb (0.0008 mg/m^3, 0.8 μg/m^3)

The primary study by Ratcliff and associates (1987) found significant changes in sperm quality indices of papaya workers exposed to EDB vapors for an average of nearly 5 years. No other health effects were apparent. A level of EDB at which no toxicity was observed (NOAEL) was not determined.

In addition to the primary study of Ratcliff *et al.* (1987), several other epidemiological studies together strongly suggest a correlation between EDB exposure and male reproductive toxicity (Ter Haar, 1980; Wong *et al.*, 1979; Wong *et al.*, 1985; Rogers *et al.*, 1981; Schrader *et al.*, 1988). This lesion appears to occur in humans at concentrations at which other toxic effects are not seen. EDB also shares some structural similarity to dibromochloropropane (DBCP), a known reproductive toxicant in human males. The evidence for male reproductive toxicity of EDB is not as strong as that for DBCP, probably because EDB is not as potent as DBCP in producing this toxic effect. However, animal studies demonstrate testicular toxicity and the number of studies indicating a connection between male reproductive toxicity and EDB exposure cannot be ignored for the development of the REL.

Chronic oral exposure of bulls to EDB results in similar toxic effects at low concentrations (equivalent to 0.9 ppm) without affecting the general health of the animal (Amir and Volcani, 1965; Amir, 1991). However, the small sample size and the lack of a dose-response effect and an observed NOAEL limits the usefulness of this study. Long-term studies of EDB toxicity in other experimental animals also lack the determination of a NOAEL (NCI, 1978; NTP, 1982). Evidence of testicular atrophy was found in other long-term studies with experimental animals, but at concentrations that also produced toxic effects in other organ systems.

For comparison with the proposed REL based on a human study, the NTP (1982) chronic inhalation study established a LOAEL (10 ppm) for liver, kidney, eyes, and the respiratory, male reproductive, and endocrine system in rats. A LOAEL was established in mice for mortality, spleen changes in females, and respiratory system toxicity. A NOAEL was not established for either species. Use of a time adjustment (6/24 hr/day, 5/7 day/week), an RGDR of 1, and a total uncertainty factor of 300 (an interspecies UF of 3, a LOAEL to NOAEL UF of 10, and an intraspecies UF of 10) resulted in an estimated REL of 6 ppb (50 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene dibromide include the use of human exposure data from workers exposed over a period of years, and the presence of the toxic endpoint (male reproductive system) in several experimental animal species. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating occupational exposure, the potential variability in occupational exposure concentration, and the limited nature of the study (fertility was not actually tested). The database for chronic toxicity of EDB in experimental animals would be enhanced if the proper doses were chosen to determine a NOAEL.

VIII. Potential for Differential Impacts on Children's Health

Little fetal toxicity was observed when pregnant rats and mice were exposed to 20 ppm EDB during gestation (Short *et al.*, 1978). Thus the REL of 0.1 ppb should adequately protect infants and children. However, we do not know if adolescent boys would be more sensitive than men to this alkylating agent. Differences in metabolic capability between infants and older children and adults may result in either more or less toxicity of EDB. Both oxidative and conjugated metabolites are toxic. Infants may produce proportionately more conjugate than oxidized metabolite relative to adults.

IX. References

Aman J, Farkas L, and Ben-Shamai MH. 1946. Experiments on the use of ethylene dibromide as a fumigant for grain and seed. Annals Appl. Biol. 33:389-395.

Amir D. 1991. The spermicidal effect of ethylene dibromide in bulls and rams. Molec. Repro. Develop. 28:99-109.

Amir D, and Ben-David E. 1973. The pattern of structural changes induced in bull spermatozoa by oral or injected ethylene dibromide (EDB). Ann. Biol. Anim. Biochem. Biophys. 13(2):165-170.

Amir D, and Volcani R. 1965. Effect of dietary ethylene dibromide on bull semen. Nature 206(4979):99-100.

Amir D, and Volcani R. 1967. The effect of dietary ethylene dibromide (EDB) on the testes of bulls. Fertil. Steril. 18(1):144-148.

Barnett LB, Lovell DP, Felton CF, Gibson BJ, Cobb RR, Sharpe DS, Shelby MD, and Lewis SE. 1992. Ethylene dibromide: Negative results with the mouse dominant lethal assay and the electrophoretic specific-locus test. Mutat. Res. 282:127-133.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Dobbins JG. 1987. Regulation and the use of “negative” results from human reproductive studies: The case of ethylene dibromide. Am. J. Ind. Med. 12:33-45.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 11/31/95).

Jones AR, and Edwards K. 1968. The comparative metabolism of ethylene dimethane-sulphonate and ethylene dibromide. Experientia 24:1100-1101.

Kulkarni AP, Edwards J, and Richards IS. 1992. Metabolism of 1,2-dibromoethane in the human fetal liver. Gen. Pharmacol., 23(1):1-5.

NCI. 1978. National Cancer Institute. Bioassay of 1,2-dibromoethane for possible carcinogenicity. Technical Report Series No. 86, DHEW Publ. no. (NIH) 78-1336.

Nitschke KD, Kociba RJ, Keyes DG, and McKenna MJ. 1981. A thirteen week repeated inhalation study of ethylene dibromide in rats. Fundam. Appl. Toxicol. 1:437-442.

NTP. 1982. National Toxicology Program. Carcinogenesis bioassay of 1,2-dibromoethane in F344 rats and B6C3F_1 mice (inhalation study). Technical Report Series No. 210, NIH Publ. no. 82-1766.

Ott MG, Scharnweber HC, and Langner RR. 1980. Mortality experience of 161 employees exposed to ethylene dibromide in two production units. Br. J. Ind. Med. 37:163-168.

Plotnick HB, and Conner WL. 1976. Tissue distribution of ^{14}C-labeled ethylene dibromide in the guinea pig. Res. Commun. Chem. Path. Pharmacol. 13(2):251-258.

Plotnick HB, Weigel WW, Richards DE, and Cheever KL. 1979. The effect of dietary disulfiram upon the tissue distribution and excretion of ^{14}C-1,2-dibromoethane in the rat. Res. Commun. Chem. Pathol. Pharmacol. 26(3):535-545.

Ratajczak HV, Thomas PT, Gerhart J, and Sothern RB. 1995. Imunotoxicologic effects of ethylene dibromide in the mouse and their modulation by the estrus cycle. In Vivo 9:299-304.

Ratcliff JM, Schrader SM, Steenland K, Clapp DE, Turner T, and Hornung RW. 1987. Semen quality in papaya workers with long term exposure to ethylene dibromide. Br. J. Ind. Med. 44:317-326.

RECT. 1988. Reviews of Environmental Contamination and Toxicology. Ethylene dibromide. 104:115-129.

REPROTOX. 1995. The REPROTOX(R) System: Reproductive Reviews of Drugs, Chemicals, Physical and Biological agents. Denver, CO: Micromedex, Inc. (Edition expires 7/31/95).

Reznik G, Stinson SF, and Ward JM. 1980. Respiratory pathology in rats and mice after inhalation of 1,2-dibromo-3-chloropropane or 1,2 dibromoethane for 13 weeks. Arch. Toxicol. 46:233-240.

Rogers BJ, Fujita JS, Najita L, and Hale RW. 1981. Reduction of sperm concentration in a population exposed to ethylene dibromide (EDB). J. Androl. 2:35-36.

Rowe VK, Spencer HC, McCollister DD, Hollingsworth RL, and Adams EM. 1952. Toxicity of ethylene dibromide determined on experimental animals. Arch. Ind. Hyg. Occup. Med. 6(2):158-173.

Schrader SM, Ratcliff JM, Turner TW, and Hornung RW. 1987. The use of new field methods of semen analysis in the study of occupational hazards to reproduction: The example of ethylene dibromide. J. Occup. Med. 29(12):963-966.

Schrader SM, Turner TW, and Ratcliff JM. 1988. The effects of ethylene dibromide on semen quality: A comparison of short-term and chronic exposure. Repro. Toxicol. 2:191-198.

Short RD, Minor JL, Winston JM, Seifter J, and Lee C. 1978. Inhalation of ethylene dibromide during gestation by rats and mice. Toxicol. Appl. Pharmacol. 46:173-182.

Stott WT, and McKenna MJ. 1984. The comparative absorption and excretion of chemical vapors in the upper, lower, and intact respiratory tract of rats. Fundam. Appl. Toxicol. 4:594-602.

Ter Haar G. 1980. An investigation of possible sterility and health effects from exposure to ethylene dibromide. In: Banbury Report 5-Ethylene Dibromide: A Potential Health Risk? Ames B, Infante P, and Reitz R. (eds). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory. pp. 167-188.

Watanabe P, Young J, Schlachter M, Zempel J, and Karbowski R. 1978. Fate of inhaled ethylene dibromide in rats. Toxicol. Appl. Pharmacol. 45:224(abstract).

Wiersma DA, Schnellmann RG, and Sipes IG. 1986. The in vitro metabolism and bioactivation of 1,2-dibromoethane (ethylene dibromide) by human liver. J. Biochem. Toxicol. 1(3):1-11.

Williams J, Gladen BC, Turner TW, Schrader SM, and Chapin RE. 1991. The effects of ethylene dibromide on semen quality and fertility in the rabbit: Evaluation of a model for human seminal characteristics. Fundam. Appl. Toxicol. 16:687-700.

Wong LCK, Winston JM, Hong CB, and Plotnick H. 1982. Carcinogenicity and toxicity of 1,2-dibromoethane in the rat. Toxicol. Appl. Pharmacol. 63:155-165.

Wong O, Utidjian HMD, and Karten VS. 1979. Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB*)*. J. Occup. Med. 21(2):98-102.

Wong O, Morgan RW, and Whorton MD. 1985. An epidemiologic surveillance program for evaluating occupational reproductive hazards. Am. J. Ind. Med. 7:295-306.